Remarks

Rejections under 35 U.S.C. §112

Claims 1-6, 8, 11 and 12 were rejected under 35 U.S.C. §112 as non-enabled. This rejection is respectfully traversed.

In order to facilitate examination, the integrin of claim 1 has been limited to CD11/CD18 integrins. This limits the scope of the integrins. The scope of the term inhibitors has been limited to the scope of claim 5. Support for these amendments is found, for example, at page 4, lines 13-15.

Data has been submitted in the application and subsequently showing the efficacy of one of these inhibitors, antibodies to Mac-1. Enclosed with this response is an abstract published in Circulation, Supp. 1, vol. 100, no. 18 November 2, 1999, number 1742, demonstrating that an equivalent effect can be obtained with a peptide inhibitor.

Rejection under 35 U.S.C. §102(e)

Claims 1-6, 8 and 10 were rejected under 35 U.S.C. §102(e) as disclosed by Simon, et al., Circulation 92(8 Suppl), 1-110 (1995) or U.S. Patent No. 5,770,198 to Coller, et al.. These rejections are respectfully traversed.

The claims are drawn to "an effective amount of a compound specifically inhibiting or reducing leukocyte adhesion or function mediated by an integrin selected from the group consisting of Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), p150,95 (CD11c/CD18), and CD11d/CD18" to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue.

As previously discussed with reference to the paper by Deitch, et al., "Effects of beta3-integrin blockade (c7E3) on the response to angioplasty and intra-arterial stenting in atherosclerotic non-human primates" Arterioscler. Thromb.Vasc. Biol. 18(11):11730-1737 (1998), the results obtained with c7E3 "were not from inhibition of intimal hyperplasia or improved artery wall remodeling.".

This antibody is known to inhibit integrin binding in cell culture, and be very effective in treating **thrombotic conditions. However, treatment of thrombotic complications (i.e., ischemia and ischemia-reperfusion injury) is not the same as, nor predictive of, treatment of patients to prevent or reduce restenosis.**

Thrombolysis causes injury due to a disruption in blood flow, followed by reperfusion, where the endothelium is intact.

Restenosis is injury arising when there is disruption in the endothelium while the blood flow remains continuous. Restenosis involves recruitment of platelets and leukocytes.

As shown by the enclosed abstract, Mickelson, et al., "Chimeric 7E3 Fab (ReoPro) decreases detectable CD11b on neutrophils from patients undergoing coronary angioplasty", J. Am. Coll. Cardiol. 33(1):97-106 (1999), this antibody decreases detectable CD11b on neutrophils but does not bind to neutrophils nor inhibit adhesion, two of the major factors involved in restenosis.

As further shown by the paper, The Eraser Investigators, "Acute Platelet Inhibition with Abciximab Does Not Reduce In-Stent Restenosis (ERASER Study), Circulation 100:799-806 (1999), this antibody did not inhibit restenosis.

This evidence demonstrates that this antibody ("Reopro") does not affect restenosis - this is not an inherent property of the antibody. Therefore neither Simon, et al., nor Coller, et al. disclose the claimed subject matter.

Rejections under 35 U.S.C. §103

Claims 1-6, 8, and 10-12 were rejected under 35 U.S.C. §103 as obvious over Ricevuit, et al., Atherosclerosis 91, 1-14 (1991) and/or Albelda, et al., FASEB J. 8:504-512 (1994), and/or U.S. Patent No. 5,770,198 to Coller,et al. or Simon, et al., Circulation (1995), in view of unidentified art for administering pharmaceutical compositions and Neumann, et al., JACC 27, 819-824 (1996). These rejections are respectfully traversed.

Simon and Coller

Simon and Coller are discussed above. They do not describe an antibody that inhibits restenosis.

Ricevuti

Ricevuti, et al., discusses the role of granulocytes in endothelial injury, as examined by reacting a monoclonal antibody to CD11b/CD18. As the examiner correctly notes, this paper relates to **ischemia and ischemia-reperfusion; not restenosis. As discussed above, and as clearly established by the ERASER study, a copy of which is enclosed, these are distinct disorders, with very different mechanisms, patient populations, outcomes, and a compound effective to treat one cannot be predicted to be efficacious in treating the other.**

Albelda, et al.

Albelda, also discusses the role of antibodies to CD11/CD18 integrins to endothelial

ligands such as intercellular adhesion molecule-1 (ICAM-1) involved in inflammation and, as the examiner has noted, "to inhibit neutrophil influx in almost every system to date including the heart and ischemia reperfusion". However, there is no mention of preventing restenosis. Many studies have shown binding to integrins - in fact, as extensively discussed above, the antibody cited by the Examiner binds to the integrin - but it does not stop neutrophil recruitment or adhesion, and it does not decrease restenosis.

Neumann, et al.

Neumann measured the presence of several molecules on platelets, before and after dilated coronary artery plaque. The results demonstrated that there was increased expression of the activated fibrinogen receptor LIBS1 on platelets as well as Mac-1 (CD11b) and L-selectin (CD62L) on neutrophils, indicating generally that there was neutrophil and platelet activation at the injured artery. There is no cause and effect here. It is just as likely these are markers arising from injury as causative agents. Therefore these results are not predictive that the claimed compounds can be used to treat restenosis.

Summary

The art cited by the examiner relates to reperfusion and ischemia (Albelda and Ricevuti), not restenosis; platelet and neutrophil activation generally following arterial activation (Neumann); and an antibody which may be cross-reactive with Mac-1 *in vitro* but is not cross-reactive *in vivo*, nor does it demonstrate any clinical effectiveness against restenosis.

Results obtained relative to ischemia and reperfusion are not predictive of results obtained in the treatment of restenosis. The mechanisms are different, the treatments are

different, the outcomes are different. Even the markers associated with restenosis are different from those associated with reperfusion. No art has been cited which would indicate that there is any teaching that ischemia is predictive of restenosis. Applicant has provided irrefutable evidence in fact that the prior art compound described as efficacious for treatment of ischemic disorders is NOT effective in treating restenosis. Therefore, compounds which relate to the treatment of ischemia and reperfusion are not encompassed by the claims. No compounds which "specifically inhibit or reduce leukocyte CD11/CD18 integrin-mediated adhesion or function", as required by claim 1, have been associated with treatment or prevention of restenosis, as required by the claims, much less is there any teaching in the cited art that would lead one skilled in the art to use compounds known for the treatment of ischemia for the treatment of restenosis, even less so with any expectation of success. Therefore the claimed subject matter cannot be obvious from the cited art.

U.S.S.N.: 08/823,999
Filed: March 25, 1997
AMENDMENT

Allowance of all pending claims 1-12 is earnestly solicited in view of the foregoing remarks and accompanying materials. All claims as pending upon entry of this amendment are attached in an appendix to facilitate review by the Examiner. **In the event the Examiner still has concerns regarding the patentability of the claims, the undersigned respectfully requests an interview at the Patent Office at which the inventors can present and explain their arguments and data in support thereof.**

Respectfully submitted,

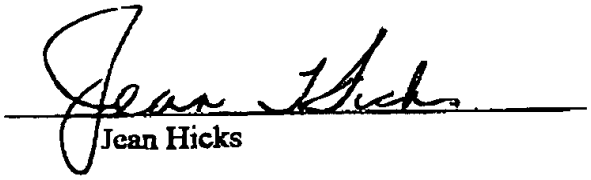
Patrea L. Pabst
Reg. No. 31,284

Date: November 30, 1999
Arnall, Golden & Gregory, LLP
2800 One Atlantic Center
1201 W. Peachtree Street
Atlanta, Georgia 30309
(404) 873-8794(Phone)
(404) 873-8795 (Fax)

CERTIFICATE OF FACSIMILE TRANSMISSION (37 CFR 1.8a)

I hereby certify that this , along with any paper referred to as being attached or enclosed, is being facsimile transmitted on the date shown below to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: November 30, 1999



Jean Hicks

811874